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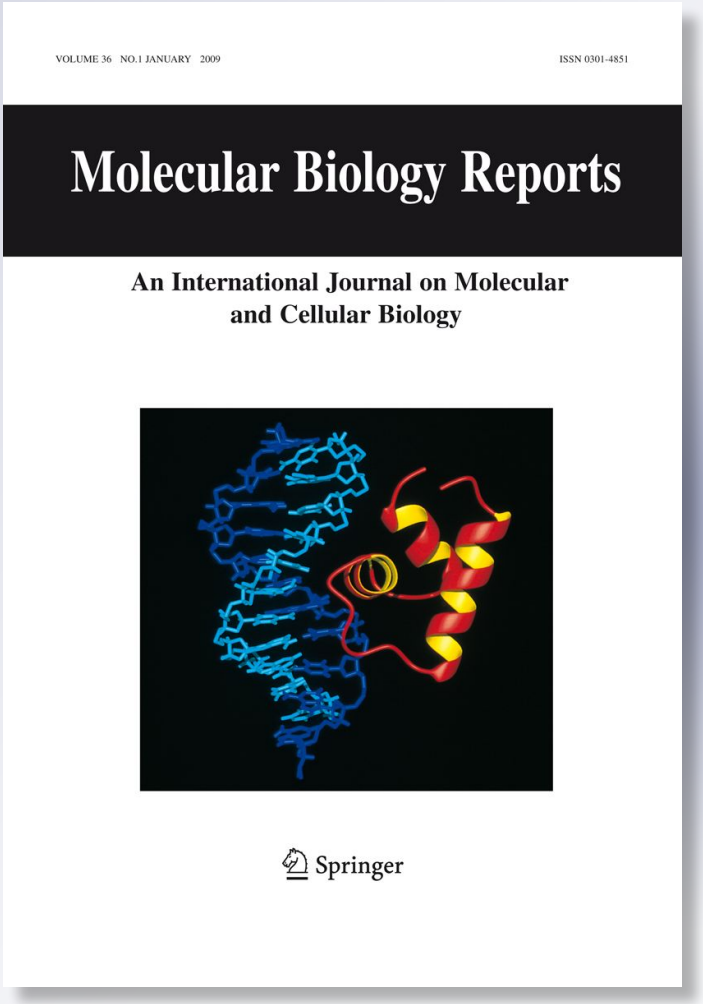

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Association of interleukin 4 VNTR polymorphism and HIV/AIDS in a north Indian seropositive patients

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Abstract Despite different efforts made to intervene with the deadly nature of HIV/AIDS, all attempts remained unsuccessful due to complexity of the viral host interactions. The solution to HIV-1 pandemic is still to come, thus to assist the efforts being made to intervene with the deadly nature of the virus, different factors responsible for the disease burdens have to be looked into a systematic manner. As a result, the present study aimed to find out the association of *IL-4* VNTR polymorphism with HIV-1 susceptibility and rate of disease progression. Three hundred cases and an equal number of sex and age matched controls were included for this study. The polymerase chain reaction assay was utilized to genotype *IL-4* VNTR. The results of this study showed statistically significant variation among cases and controls in the distribution of the *Rp2/Rp2* genotype (OR = 0.36, 95% CI = 0.18–0.69; *P* value = 0.0014) indicating, thereby, a possibility of reduced risk of HIV-1 susceptibility. Thus, *Rp2/Rp2* genotype of the *IL-4* might have a role to play in reducing risk of HIV-1 susceptibility among a north Indian population.

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Keywords HIV/AIDS · *IL-4* VNTR · Disease progression

Introduction

The human immunodeficiency virus (HIV) epidemic, first documented in the early 1980s has since expanded to include an estimated 2.7 million cases of infection and 2.0 million HIV related deaths worldwide in the year 2007 alone. Current estimates indicate that 32.5 million persons worldwide are infected with HIV, and that approximately 89,000 new infections occur each day. Sub-Saharan Africa remains the most heavily affected region, accounting for 71% of all new HIV infections in 2008 [1]. Since the first report of HIV infection in India in 1986, the virus has spread all over the country although there is geographic variation. There are estimated 5.1 million people infected with HIV with an overall estimated adult prevalence below 1% [2].

IL-4 is a prototypic member of Th2 cytokines and is a potent anti-inflammatory cytokine. It reduces the production of proinflammatory cytokines and destructive enzymes by monocytes [3]. The *IL-4* gene is located on the long arm of chromosome 5 (q23–31) in a cluster of other cytokine genes (*IL-3*, *IL-5*, *IL-9*, *IL-13*, and *IL-15*, granulocyte colony-stimulating factor, and interferon regulatory factor) [4]. It is also a key T helper-2 cytokine that down regulates and up regulates CCR5 and CXCR4, respectively, the main coreceptors for HIV [5]. This gene contains a variable number of tandem repeat polymorphism located in third intron. Interons are a primary transcript that is removed by splicing during RNA processing and is not included in the mature, functional mRNA. However, genetic polymorphisms of interons in *IL-4* and *IL-1 RA* genes have been

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reported to modulate a number of diseases in the literature. *IL-4* VNTR consists of 70-bp repeats in intron-3, a rare allele with two repeats (R*p1/Rp1*) and much rarer with four repeats (*Rp2/Rp2*). It is a growth costimulator for B and T cells, mast cells, erythroid progenitor, and myeloid progenitors. Earlier studies have reported that *IL-4* inhibits the release of inflammatory mediators, such as TNF-α, IL-6, and IL-1α from activated monocytes. The homozygous *Rp1/Rp1* genotype has been reported to modulate risk of bladder cancer [6]. Maier et al. [7] reported lack of association of *IL-4* interon 3 VNTR polymorphism (*Rp1/Rp1* genotype) with type 1 diabetes mellitus. On the other hand Achyut et al. [8] demonstrated a significant association this genotype of *IL-4* interon 3 VNTR polymorphism with increased risk of type 2 diabetes mellitus as well as its associated complication with north Indian population.

During HIV infection the host responds with a complex series of immune reactions to neutralize invading pathogens, repair injured tissues, and promote wound healing [9]. Excessive production of cytokines, such as TNF, IL-1β, and high mobility group B1 (HMGB1), however, can be more injurious than the inciting event, initiating diffuse coagulation, tissue injury, hypotension and death [10, 11]. The inflammatory response is balanced by anti-inflammatory factors including the cytokines IL-10 and IL-4, soluble TNF receptors, IL-1 receptor antagonists, and transforming growth factor (TGF-β).

Soriano et al., reported that variants of host genes are important determinants of susceptibility to HIV-1 infection and its rate of progression to AIDS [5]. In determining important mechanisms for protection from HIV infection, individuals who remain seronegative despite multiple exposures to the virus represent an extremely valuable study population. The observation that in some people repeated exposure to HIV does not result in infection could be explained in several ways. First, low viral loads or the presence of replication-defective virus strains in the primary partner could result in a reduced rate of transmission. Second, resistance to infection in an exposed uninfected individual may be caused by the absence or reduced susceptibility of target cells. Finally, protection from infection may be mediated by HIV-specific antibodies or cells that are capable of inhibiting infection and/or viral spread. Based on the latter mechanism, repeated exposures could potentially lead to enhancement of antiviral immunity, functioning much like a booster vaccination [12].

Several findings underscore the potential importance of humoral immune responses in protection against HIV infection. Macaques can be protected against intravenous and mucosal viral challenge following passive transfer of neutralizing antibodies against the SIV-HIV chimeric virus, SHIV [13–15]. In addition, circulating antibodies against the viral core antigen p24 can be detected shortly after infection and may assist in the control of viral replication in vivo [16]. IL-4 as one of the Th2-type anti-inflammatory cytokines is involved in inducing humoral immunity and plays a role in inducing IgG1 antibodies [17] and thus *IL-4* VNTR could be considered as a candidate gene to be studied to evaluate its effect on HIV susceptibility and its progression to AIDS. Thus, we hypothesized that *IL-4* as one of the antiinflammatory cytokine genes could have positive role in reducing HIV susceptibility and rate of disease progression among north Indian seropositive patients.

The aim of the present study was to analyze the association of *IL-4* VNTR polymorphism on HIV/AIDS susceptibility and disease progression on north Indian seropositive patients.

Materials and methods

Blood samples of 300 HIV patients were collected in EDTA-anticoagulated tube from the Post Graduate Institute of Medical Education and Research, Chandigarh, all of them from north Indian population. Inclusion criteria for collecting blood samples included all patients who were HIV seropositive, had never started highly active antiretroviral treatment (HAART) and their age ranged between 18 and 60 years. Seropositive patients under HAART treatment were excluded from the study. An equal number of age and sex matched control samples were collected from the same institute. An inclusion criterion for recruiting control samples was being seronegative for HIV-1 test and age ranged between 18 and 60 years. Informed consent was obtained from both cases and controls as per the approved guidelines of the ethical committee of Post Graduate Institute of Medical Education and Research, Chandigarh. While the detailed history of each patient was obtained from patients' record, interviews were conducted to get relevant information from controls. This study was approved by the ethical committee of the Post Graduate Institute of Medical Education and Research, Chandigarh.

Genotyping of IL-4 interon 3 VNTR

Genomic DNA was extracted from peripheral blood lymphocytes by the standard phenol- chloroform method. The *IL-4* VNTR polymorphism of 70 bp was amplified using primers forward 5′-AGGCTGAAAGGGGGAAAGC-3′and reverse 5′-CTGTTCACCTCAACTGCTCC-3′. The PCR amplification was performed in 25 µl volume containing 100 ng of genomic DNA, 0.2 mM of mixed dNTP, 20 pmol of each primer 1.5 U Taq polymerase, 10× KCl and 1.5 mM $MgCl_2$. The amplification conditions utilized were initial denaturation of 95^0 C for 5 min followed by 30

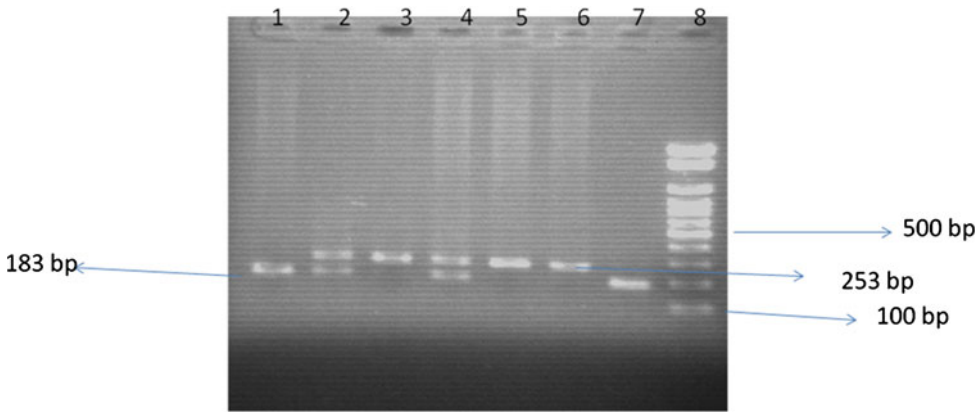

Fig. 1 PCR-VNTR representative agarose gel picture of *IL-4* gene of HIV seropositive subjects

Lane 8 100 bp DNA Marker
Lanes 1 and 7 *Rp1/Rp1* 183 bp
Lanes 2 and 4 *Rp1/Rp2* 183 and 253 bp
Lanes 3,5, and 6 R*p2/Rp2* 253 bp

cycles of each with denaturation at 95°C for 45 s, 65°C for 45 s, 72°C for 10 s, and a final extension of 72°C for 7 min. Alleles of 183 bp (two repeats) and 253 (three repeats) were designated as *RP1* and *RP2,* respectively and were analyzed by resolving on 2% agarose gel electrophoresis [18] (Fig. 1).

Statistical analysis

Relevant data of cases such as age, sex, CD4 count, transmission route, occupation, type and number of opportunistic infections were tabulated to compute the association with the host genetic factors. However, the control samples in this study were healthy and only their age, sex and sexual behavior were tabulated. The effect and association of the *IL-4* VNTR polymorphism on HIV susceptibility and disease progression was analyzed by computing odds ratio (OR) and 95% confidence interval (CI). The statistical analysis was performed using Epi-Info software (Epi-Info, version 3.5.1. Center for Disease Control and Prevention, Atlanta, GA, USA, August 13, 2008) and software SPSS version 11.5 (SPSS, Chicago, IL). Chi square (χ^2) test was utilized to check for the Hardy–Weinberg's equilibrium. Significance was set at $P < 0.05$ except for stage and genotype interaction where significance was set at $P < 0.01$.

Results

The demographic characteristic of study subjects is given in Table 1. Three hundred cases and age and sex matched controls had participated in this case control study. There was no significant variation in the mean age of study subjects. The mean age of cases was 35.23 ± 8 and that of controls, it was 36.17 ± 10. The number of women in cases and controls were 107 (35.7%), 105 (35%) respectively. Among 300 HIV seropositive cases, 26 (8.7%) were labourers, 55 (18.3%) were farmers, 65 (21.7%) drivers and

Table 1 Demographic characteristics of study subjects

	Cases	Controls	*P* value
Mean age ± SD	35.23 ± 7.6	36.17 ± 10.0	0.197*
Place			
Urban	96 (32%)	106 (35.3%)	
Rural	214 8%)	196 (64.7%)	
Sex			
Male	193	195	
Female	107	105	0.93*
Transmission route in cases			
Heterosexual	277		
Needle sharing	4		
Blood donation	5		
Homosexual	1		
Unknown	13		
Mean of CD4 count at each stage of cases			
I	498		
II	384		
III	259		
IV	116		
Occupation of cases			
Laborers	26		
Farmers	55		
Truck driver	65		
House wives	89		
Others	65		

* $P > 0.05$

65 (21.7%) working on other different sectors and 89 (29.70) were house wives. When the transmission route of HIV was studied, heterosexual transmission accounted for 92.3% of the transmission followed by contaminated needle 1.7 and unidentified transmission which accounted 1.3% only. Acquiring HIV during blood transfusion and men who had sex with men (MSM) accounted 1.7 and 0.63% respectively. Cases belonging to the unknown category were involved in more than one possible routes of transmission and did not exactly know the source of their infection. Cases were tabulated regarding their marriatal status. Of all 107 women cases, 12 (11.2%) of them were not married. Similarly, of all the 193 males, only 23 (11.9%) were unmarried. Among 95 married women, 18 lost their spouses (all of them by HIV, except one). Among 170 married men, 20 lost their spouses by HIV/AIDS, 20 of the spouses were seronegative, 85 seropositive and the serological status of the remaining 45 male spouses were not known.

As per the WHO staging guideline cases at all the four stages of HIV/AIDS were found. Of all the 300 seropositive cases, 27 (9%) were at stage I, 54 (18%) at stage II, 73 (24.3%) at stage III and 146 (48.7%) were at stage IV of the disease. The mean CD4 counts for stages I, II III and IV were 498.37, 383.87, 258.87 and 115.71 respectively.

The Hardy–Weinberg's equilibrium was analyzed by using χ^2 test. Genotype and allelic frequencies were in line with the Hardy–Weinberg's equilibrium $P > 0.05$. The percentage of the *IL-4* interon 3 VNTR genotype distribution for both cases and controls is given in Table 2. The frequency of *Rp1/Rp1* in cases was 12.7% as compared to 5.3% in controls. The frequency of heterozygous genotype *Rp1/Rp2* was greater in cases (33.3%) from that in controls (31.3%). On the other hand, the homozygous *Rp2/Rp2* genotype was smaller in cases (54%) than that in controls (63.3%). The heterozygous *Rp1/Rp2* and the homozygous *Rp2/Rp2* genotype showed statistically reduced risk for susceptibility of HIV with OR 0.45, 95% CI 0.22-0.90 and OR 0.36, 95% CI 0.18–0.69, respectively with *P* value < 0.005. Of all the 27 cases at stage I, 9 (59.3%) were having *Rp2/Rp2,* on the other hand of all 146 seropositive cases at stage IV, only 77 (51.4%) were having the *Rp2/Rp2* genotype. Detailed genotype distribution and stages of the disease is summarized in Table 3.

When disease progression and genotype frequency was computed, it was found that of all the 4 patients who were at stages II and III after 10 years of seroconversion all of them possessed *Rp2/Rp2* genotype and they remained to be long term non progressors (LTNP) after 10 years of seroconversion. No long term non progressors were found with the other two genotypes. Time of progression with respect to genotype frequency is given in Table 4.

Discussion

In the present study the genotype frequency of *Rp2/Rp2* was associated with statistically significant reduced risk of HIV susceptibility (OR = 0.36, 95% CI 0.18–0.69, with *P* value 0.0014. Moreover, all of the 4 long term non progressors (those who did not attain stage IV of AIDS after 10 years of seroconversion) possessed this genotype, which was 100% availability and no long term non progressor was observed with other genotypes indicating the role of *Rp2/Rp2* genotype in decreasing the risk of HIV susceptibility and rate of disease progression.

IL-4 and its receptor *IL-4R* are very important candidate genes that affect susceptibility to HIV infection and its progression to AIDS due to two reasons. First, apart from its effects on B cells to induce Ig isotype switching to IgE, *IL-4* induces differentiation of CD4+ Th cells into Th2 cells, which, in turn, are characterized by production of IL-4 and lack of interferon γ (IFN-γ) production. Th1 cells are characterized by production of IFN-γ and absence of IL-4 production. In addition, *IL-4* inhibits generation of Th1 cells, while *IFN-γ* inhibits generation of Th2 cells [19, 20].

Though the exact function of the *Rp1/Rp2* interon 3 polymorphism is not known [21], Sei et al. [16] showed that higher virus replication correlated with increased IL-4 levels in lymph nodes from infected children. Moreover, there existed a report that IL-4 has differential effects on the expression of *CCR5* and *CXCR4* and that it also stimulates intracellular pathways leading to increased HIV-1 production [22]. Contrary to this, higher expression of IL-4

Table 2 Genotype and allelic frequency of IL-4 VNTR among the study subjects

	Cases	Controls	OR (95% CI)	*P* value
IL-4 genotypes				
Rp1/Rp1	38 (12.7%)	16 (5.3%)	Ref. 1.0	
Rp1/Rp2	100 (33.3%)	94 (31.3%)	0.45 (0.22–0.90)	0.021
Rp2/Rp2	162 (54.0%)	190 (63.3%)	0.36 (0.18–0.69)	0.0014
Allelic frequency				
R1	0.3	0.21	1.0 Ref	
R2	0.7	0.79	0.62 (0.31–1.24)	0.19

OR was computed using Epi Info version 3.5.1. (center for disease control and prevention)

Table 3 Genotype distribution in respect to each stage of HIV/AIDS and relative OR

Stages of HIV	Genotypes of *IL-4*	n/c	OR (95% CI)	*P*
I	*Rp1/Rp1*	3/16	1.0 Ref	–
	Rp1/Rp2	8/94	0.50 (0.14–1.70)	0.37
	Rp2/RP2	16/190	0.49 (0.16–1.54)	0.20
II	*Rp1/Rp1*	8/16	1.0 Ref	–
	Rp1/Rp2	15/94	0.32 (0.10–0.98)	0.03
	Rp2/RP2	31/190	0.33 (0.12–0.92)	0.03
III	*Rp1/Rp1*	14/16	1.0 Ref	–
	Rp1/Rp2	19/94	0.23 (0.09–0.60)	0.001*
	Rp2/RP2	40/190	0.24 (0.10–0.57)	0.00050*
IV	*Rp1/Rp1*	13/16	1.0 Ref	–
	Rp1/Rp2	58/94	0.76 (0.32–1.82)	0.64
	Rp2/RP2	75/190	0.49 (0.21–1.13)	0.10

OR was computed using Epi Info version 3.5.1. (center for disease control and prevention)

* *P* value less than 0.05 and set as significant

Table 4 Frequency of *IL-4* VNTR genotype and time of HIV progression to AIDS

Year after sero conversion	Genotypes	Stage I	Stage II	Stage III	Stage IV
1–2	*Rp1/Rp1*	1	3	9	7
	Rp1/Rp2	3	5	6	20
	Rp2/Rp2	3	10	18	25
2–5	*Rp1/Rp1*	2	2	4	5
	Rp1/Rp2	5	10	11	34
	Rp2/Rp2	11	16	18	42
6–10	*Rp1/Rp1*		3	1	
	Rp1/Rp2			2	3
	Rp2/Rp2	2	2	3	8
>10	*Rp1/Rp1*				1
	Rp1/Rp2				1
	Rp2/Rp2		3	1	

was reported to be associated with a better prognosis in Thai population [23]. At present, the reason for the discrepancy among different studies is not clear, but it may be due to the differences in study design (sero-conversion/crosssectional, marker/endpoint of disease progression, duration of follow-up, etc.) or difference in the frequency of the genotypes. However, allele *Rp2* was reported to have a protective role in autoimmune diseases [23]. Even if, a multitude of factors, including immunological, genetic, viral and environmental, can potentially contribute to the rate of HIV disease progression [24], it could be inferred from this study that *IL-4* VNTR as a host genetic factor seems to have a greatest role in reducing disease progression and susceptibility. It is stated that HIV infection stimulates immune activation and the latter too activates the former. HIV-infected individuals display elevated markers of activation and/or apoptosis on CD8+ and CD4+ T, as well as B cells, NK cells and monocytes [25–28]. On the other hand, it is demonstrated that high levels of proinflammatory cytokines, such as tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6) and interleukin 1 beta (IL-1β) in both plasma and lymph nodes, are observed from the early stages of HIV-1 infection [29–31] and facilitates disease progression to AIDS via activation of viral replication.

From the results of the present study, it is possible to conclude that *IL-4* VNTR *Rp2/Rp2* genotype may have likely a role to play in increasing IL-4 level in the serum that antagonizes the level of proinflamatory cytokines that in turn reduces viral activation and replication, as a result, rate of disease progression could be slower. This could be strengthened by the adverse effect of immune activation in HIV pathogenesis that accounted for the observations linking more rapid disease progression in Kenyan prostitutes with frequent inter current infections and related immune activation [32]. Moreover, it has been stated that the immune activation caused by HIV is a persistent chronic hyperactivation of both CD4 and CD8 T cells. Activated by strander CD4 T cells that appear as a result of HIV replication may be more sensitive to HIV infection

and may thereby, create positive feedback mechanism, resulting in further enhancement of HIV replication [33].

As far as our knowledge goes, this is the first case control study that attempted to evaluate the association of *IL-4 VNTR* polymorphism on HIV/AIDS, and thus, it is hardly possible to provide clear cut explanations as to why the *RP2/RP2* genotype reduces the risk for susceptibility and disease progression. As a result further studies on the role of *IL-4* VNTR polymorphism in relation to HIV/AIDS are warranted with large cohort on different ethnic backgrounds by considering exposed and uninfected control groups. Furthermore, the role and effect of *IL-4* VNTR polymorphism needs to be confirmed through in vivo expression on biological animals, so that the function of each allele could be explained and understood. Since this is the first report on *IL-4* VNTR polymorphism and HIV/AIDS, shortage of information on *IL-4* VNTR polymorphism and HIV/AIDS made the explanation of the *Rp2/Rp2* genotype association with protective role not to be precise. Indeed one of the draw backs of the present study was inability to recruit exposed and non infected individuals as control groups; however, small sample size and unwilling of these study subjects to participate for this study shortened the study from being completed. This study is part of our continuing studies on impact of gene polymorphism on HIV-1 disease progression to AIDS among north Indian seropositive patients [34].

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